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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,642	01/28/2004	Anthony Atala	105447-2	4621

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 09/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/766,642	ATALA ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-33* is/are pending in the application.

4a) Of the above claim(s) *14-22 and 30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12,13,23-29 and 33* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-13 and 23-29, in the reply filed on 27 July 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The restriction requirement is made FINAL.

Response to Arguments/Amendments

Applicant's arguments filed 27 July 2005 have been fully considered but they are not persuasive. Amendments to claims 1 and 23 have been entered. Claim 11 has been cancelled. New claim 33 has been entered. Claims 1-10 and 12-33 remain pending in the current application, with claims 14-22 and 30-32 being withdrawn from consideration.

Claim Objections

Claim 13 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Applicants have amended claim 1 to require VEGF to be the angiogenesis-modulating agent; therefore claim 13 is redundant and repetitive.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 and 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 1 is confusing as written, particularly with regards to the phrase, "a VEGF angiogenesis modulating agent." It is not clear if VEGF *is* the angiogenesis modulating agent, or if reference is being made to a genus of "VEGF angiogenesis modulating agents." It would remedial to change the language to, "...transfecting a population of cells with a plasmid encoding the angiogenesis modulating agent VEGF;..."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 12 and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Penn et al (US 2004/0161412 A1), as fully supported by provisional applications 60/424,065 & 60/405,274.

Applicant's claim 1 is directed to a method of organ augmentation comprising the steps of: transiently transfecting a population of cells with a plasmid encoding a VEGF angiogenesis modulating agent; and implanting the transiently transfected cells into a target tissue region where the cells will express the angiogenesis modulating agent thereby inducing assimilation and differentiation of cells in the target region and augmenting organ function. Claim 3 requires the population of cells to comprise undifferentiated cells. Claim 12 requires the cells to be myoblasts. Claim 13 requires the angiogenesis modulating agent to be VEGF.

Penn et al teach a method of tissue regeneration and organ augmentation, specifically augmentation of an infarcted myocardium, comprising transfecting a population of skeletal myoblasts (undifferentiated cells) with a VEGF expression vector, and then implanting the transfected cells into the myocardium, thereby stimulating stem cell differentiation and regenerating ischemia damaged tissue, particularly improving left ventricle function (See Pg. 2, paragraph 0020 & Pg. 3, paragraphs 0044-0045). Penn et al teach the VEGF expression vector can be introduced into the target cells by viral vector-based methods, or by non-viral gene delivery methods, particularly by plasmid DNA transfection (See Pg. 7, paragraph 0092). Penn et al also teach that the VEGF can be transiently expressed for any suitable and defined length of time (See Pg. 8, paragraph 0100-0102). Penn et al teach that local and transient expression of VEGF is sufficient to induce neovascularization and minimize systemic effects and hemangioma formation (See Pg. 1, paragraph 0004). Therefore the reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10, 12-13, 23-29 & 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atala et al (US Patent 6,479,064), in view of Penn et al (US 2004/0161412 A1), further in view of Cima et al (J. Biomed Engineering, 1991) and Griffith-Cima (US Patent 5,709,854).

Atala et al teach a method of augmenting organ function comprising culturing a population of endothelial cells on a three-dimensional matrix to form an organ construct capable of differentiation *in*

vivo to replace or augment organ function; and seeding a second population of parenchymal cells onto the matrix; and co-administering the cell populations by implanting the organ construct *in vivo* at a target site to induce assimilation and differentiation of cells in the target region (See Atala et al, col. 2, ln 19-52; col. 12, ln 37-49; and Claims 1 & 14). Atala et al use endothelial cells in order to form a primitive vascular system, therefore it appears Atala et al intends to use vascular endothelial cells (See Atala et al, col. 2, ln 19-52); the parenchymal cells can comprise undifferentiated muscle stem cells (See Atala et al, col. 9, ln 7-19) (Claims 3-7). Atala et al teach either the endothelial cells or the parenchymal cells can be transfected, by any means known in the art, to produce a gene product beneficial for transplantation, such as angiogenesis modulating agents IL-1 or IL-2 (See Atala et al col. 10, ln 4-23 & col. 14, ln 24-30). The three-dimensional matrix can be implanted into the subject, therefore it acts as a pharmaceutically acceptable carrier; it can comprise decellularized tissue, it can further be treated with collagen or other materials to aid in cellular attachment and growth (See Atala et al, col. 11, ln 30-38 & col. 12, ln 18-23) (Claims 8-9).

Though Atala et al teach a general method of forming an organ construct comprising culturing two different cell types on a single matrix, intending for implantation into a subject, they are relatively general on the types of cell that can be used, teaching that endothelial cells and parenchymal cells are preferred embodiments. Penn et al teach a method of tissue regeneration and organ augmentation, specifically augmentation of an infarcted myocardium by improving left ventricle function, comprising transfecting a population of skeletal myoblasts (undifferentiated cells) with a VEGF expression vector, and then implanting the transfected cells into the myocardium, thereby stimulating stem cell differentiation and regenerating ischemia damaged tissue (See Pg. 2, paragraph 0020 & Pg. 3, paragraphs 0044-0045). One of ordinary skill in the art will recognize that in performing transfections, some cells will not be successfully transfected, due to failure to uptake the plasmid, or rapid rejection of the plasmid; therefore, though Penn et al teach transfecting a population of myoblasts, it will be understood that both

successfully transiently transfected cells and non-transfected cells will be injected (which applicant calls two separate populations of myoblasts, wherein the non-transfected cells comprise the first population, and the transiently transfected myoblast cells comprise the second population). Penn et al teach the VEGF expression vector can be introduced into the target cells by viral vector-based methods, or by non-viral gene delivery methods, particularly by plasmid DNA transfection (See Pg. 7, paragraph 0092). Penn et al also teach that the VEGF can be transiently expressed for any suitable and defined length of time (See Pg. 8, paragraph 0100-0102) (Claim 1). Penn et al teach that local and transient expression of VEGF is sufficient to induce neovascularization and minimize systemic effects and hemangioma formation (See Pg. 1, paragraph 0004). Additionally, though Penn et al teach transfecting the myoblast cells, it would have been obvious to one skilled in the art to transfect either the endothelial cells or the myoblasts (parenchymal cells) for seeding onto the matrix. One skilled in the art would have been motivated to transiently transfect either cell population because transient expression by either cell population would result in the presence of VEGF. One would have expected success because Atala et al teach that either cell population can be transfected.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to form a construct, such as done by Atala et al, using the transfected myoblast populations of Penn et al in order to form an implant to replace ischemia damaged myocardium tissue, thereby augmenting the overall function of the heart, particularly improving left ventricle function, as taught by Penn et al (Claims 23, 24, 28, 29). As stated above, because the myoblasts of Penn et al effectively comprise what applicant calls two populations of cells, a first population of non-transfected myoblasts, and a second population of transiently transfected myoblasts, would be seeded onto the matrix of Atala et al (Claim 27). One of ordinary skill in the art would have been motivated to use the transiently transfected myoblast population of Penn et al (which also comprises some non-transfected cells) as the parenchymal cells in the construct of Atala et al in order to form a muscle construct for implantation, such

in order to strengthen walls of the heart muscle damaged by ischemia. By completely replacing ischemia damaged myocardium tissue with the tissue construct described above, one would improve over Penn et al's method of merely introducing new cells to strengthen the tissue at the site of damage, by completely replacing the damaged tissue with a functional tissue equivalent, thereby eliminating risks of future problems due to the presence of weakened tissue. Therefore, by implanting the above mentioned tissue construct, one would augment the function of the heart by removing the damaged tissue and replacing it with a functional tissue equivalent. One would expect success because Penn et al teach the transiently transfected VEGF-expressing myoblast cells stimulate stem cell differentiation and regenerate ischemia damaged tissue (See Penn et al, Pg. 2, paragraph 0020 & Pg. 3, paragraphs 0044-0045). With regards to the length of time the VEGF is produced, Penn et al teach that the duration of the transient expression is a result effective variable that would be routinely optimized by one of ordinary skill in the art (See Penn et al, pg. 8, paragraphs 0099-0102). Penn et al teach that the cells can be transiently transfected so as to express a therapeutic amount of VEGF; Penn et al further teaches that it is well within the scope of one skilled in the art to determine the appropriate therapeutic amount on an individual basis, as factors such as size, age, sex, presence of other drugs, and concentration of the active drug, all effect the optimal duration of expression. Therefore, the duration of the transient expression of VEGF would have been routinely optimized by one of ordinary skill in the art at the time the invention was made, especially with lack of evidence to the contrary, submitting the claimed time period is critical (Claim 2).

Atala et al teach using three-dimensional matrices derived from decellularized tissues; however it also would have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively use three-dimensional matrices made from polymers such as polylactic acids or polyglycolic acids or combinations thereof (PLAs, PGAs, or PLGAs), such as those described by Cima et al (See Cima Pg. 145, col. 1) (Claims 10, 26). One of ordinary skill in the art would have been motivated to use a polymeric matrix because Cima et al teach they are biocompatible and degradable; they are capable of

allowing vasculogenesis, in the case of organ construction, and come pre-made in a variety of shapes, sizes, and are available in a variety of resorptive rates (See Cima et al, Pg. 145, col. 1). One would have expected success because Cima et al teach successfully using polymeric matrices to develop cartilage constructs for transplantation as well as liver constructs for transplantation.

Griffith-Cima et al provide another alternative to decellularized tissue in US Patent 5,709,854, where they disclose a matrix comprised of hydrogel, in which cells can be cultured and then subsequently injected into a patient to form an organ equivalent or tissue construct (See col. 1, ln 27-58) (Claim 25). Therefore one of ordinary skill in the art would have been motivated to use a matrix comprised of hydrogel in the method of Atala et al in place of decellularized tissue. One of ordinary skill in the art would have been motivated to use an injectable hydrogel matrix to avoid surgical implantation and pre-shaping/manipulation of the matrix, as is required with solid matrices. Additionally, Griffith-Cima et al teach the hydrogel is biocompatible, biodegradable, and can successfully be used to deliver large amounts of cells into a patient. One would have expected success because Griffith-Cima et al teach successfully forming cartilaginous structures using chondrocyte populations embedded in hydrogel; therefore one would expect similar success with any cell type, including the transfected populations of the method of Atala et al and Penn et al.

Still further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to implant the tissue constructs described above in multiple locations in the myocardium (Claim 33). One of ordinary skill in the art would have been motivated to implant the tissue constructs in any and all locations where myocardium tissue had been damaged by ischemia in order to replace the damaged tissue with a functional tissue equivalent in order to augment the function of the heart by removing ischemic tissue. One would have expected success because it is well recognized in patent law that replication or duplication of parts (such as implanting multiple tissue constructs) is prima facie obvious, e.g. see *In re Harza,* 274 F.2d 669, 124 USPQ 378 (CCPA 1960).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5, 8, 10, 23-26 and 29 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11, 16, 17 & 18 of copending Application No. 10/292,166. Although the conflicting claims are not identical, they are not patentably distinct from each other because though the claims of co-pending application '166 do not require one of the populations of cells to be transfected with a plasmid encoding an angiogenesis modulating agent, the claims of the current application fall into the scope claimed by co-pending application '166 as the current claims are directed to a method for augmenting organ function comprising: perfusing at least one population of cultured cells on or into a matrix material, such that cells attach to the matrix material; culturing the cells in the matrix material to produce a tissue layer capable of differentiating into an artificial organ construct, thereby producing a three-dimensional biomatrix; and implanting the three dimensional biomatrix into at least one target site in the organ, such that the tissue layer of the three dimensional biomatrix differentiates to provide a gain of function to the organ, thereby augmenting organ function at the target site (co-pending application claim 11, current claims 1, 5, 8, 23 and 29); wherein the

matrix is decellularized tissue (co-pending application claim 16; current claims 24), hydrogel (co-pending application claim 17; current claim 25), or a polymer (co-pending application claim 18; current claims 10 and 26). Thus it would have been obvious to one of ordinary skill in the art to first transfect one of the populations of cells with a plasmid encoding an angiogenesis modulating agent, making the current claims obvious over the claimed method of '166. One of ordinary skill in the art would have been motivated to first transfect a population of cells with a plasmid encoding for an angiogenesis modulating agent in order to increase the expression of the angiogenesis modulating agent in the construct formed by the present methods. One would have expected success because it is well known in the art that transfecting a cell, or population of cells, with a plasmid encoding an angiogenesis modulating agent would successfully result in increased expression of the transfected DNA.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant has argued that the amendment to the claims has rendered the obvious-type provisional double patenting rejection moot. However, applicant's arguments do not clearly point out the patentable novelty which he or she thinks the claims present over the co-pending application. Further, they do not show how the amendments avoid such rejection.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing

date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651